HEALTH EFFECTS OF

EXPOSURE TO

ENVIRONMENTAL TOBACCO SMOKE

REVISIONS TO FINAL DRAFT

JUNE 9, 1997

Office of Environmental Health Hazard Assessment
California Environmental Protection Agency

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Deletions in strikeout, additions in underline unless noted otherwise

Revisions to Executive Summary

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Relative risk estimates associated with some of these endpoints are small, but because the diseases are common the overall impact can be quite large. A "weight of evidence" approach has been used to describe the body of evidence ~~for an effect and to support a~~ to conclude ~~sion as to~~ whether or not ETS exposure is causally associated with a particular effect.

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Effects with Suggestive Evidence of a Causal Association with ETS Exposure

Developmental Effects
Spontaneous abortion
Adverse impact on cognition and behavior

Respiratory Effects
~~Asthma exacerbation in adults~~
Exacerbation of cystic fibrosis
Decreased pulmonary function

Carcinogenic Effects
Cervical cancer

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Change second sentence to:

A relative risk estimate of 1.3 for heart disease mortality in nonsmokers is supported by the collective evidence; this corresponds to a lifetime risk of death of roughly 1 to 3% for exposed nonsmokers and could perhaps explain as many as 4,000 deaths annually in California.

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ETS exposure produces a variety of acute effects involving the upper and lower respiratory tract. In children, ETS exposure can exacerbate asthma, and increases the risk of lower respiratory tract illness, and acute and chronic middle ear infection. ~~ETS may also exacerbate asthma in adults.~~ Eye and nasal irritation are the most commonly reported symptoms among adult nonsmokers exposed to ETS. Odor annoyance has been demonstrated in several studies.

TABLE ES.2

ESTIMATED ANNUAL MORBIDITY AND MORTALITY IN NONSMOKERS ASSOCIATED WITH ETS EXPOSURE [a]

Condition	Number of People or Cases	
	in the U.S.	in California[a]
Developmental Effects		
Low birthweight	≈ 9,700 - 18,600 cases[b]	≈ 1,200 - 2,200 cases[b]
Sudden Infant Death Syndrome (SIDS)	≈ 1,900 - 2,700 deaths[b]	≈ 120 deaths[b]
Respiratory Effects in Children		
Middle ear infection	0.7 to 1.6 million physician office visits[b]	78,600 to 188,700 physician office visits[b]
Asthma induction	8,000 to 26,000 new cases[c]	960 to 3120 new cases[c]
Asthma exacerbation	400,000 to 1,000,000 children[c]	48,000 to 120,000 children[c]
Bronchitis or pneumonia in infants and toddlers (18 months and under)	150,000 to 300,000 cases[c] 7,500 to 15,000[c] hospitalizations 136 - 212 deaths[c]	18,000 to 36,000 cases[c] 900 to 1800 hospitalizations 16 - 25 deaths
Cancer		
Lung	3000 deaths[c]	360 deaths[c]
Nasal sinus	N/A[db]	N/A[db]
Cardiovascular Effects		
Ischemic heart disease	35,000 - 62,000 deaths[c]	4,200 - 7,440 deaths

[a] As discussed in Chapter 1, there are uncertainties, which are difficult to quantify, associated with these estimates. ~~The exceptions are~~ They are based on estimates of attributable risk, the maximum proportion of the disease occurrence that potentially would be eliminated if exposure were prevented.

[b] California estimates for low birthweight, SIDS, and otitis media ~~which~~ are provided in Chapters 3, 4, and 6 respectively. ~~For these cases the sources cited provided the odds or risk ratios serving as the basis for the analyses.~~ US estimates are obtained by dividing by 12%, the fraction of the U.S. population residing in the California.

[c] Estimates of mortality in the US for lung cancer and respiratory effects, with the exception of otitis media, from US EPA (1992). US range for heart disease mortality reflects estimates reported in Wells (1994, 1988), Glantz and Parmley (1991), Steenland (1992).[a] California predictions are made by multiplying the U.S. estimate by 12%, the fraction of the U.S. population residing in the State.

[db] Estimates of the impact of ETS exposure on the occurrence of nasal sinus cancers are not available at this time.

Revisions to Chapter 1

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Animal models for ETS exposure have been recently developed and ~~a number of~~ studies using such models are being released ~~are currently underway~~ (Witschi et al., 1997a, b)~~TRDRP, 1991; 1992)~~. Typically, "sidestream" smoke is produced from the lit end of a cigarette through which air is drawn to separate "mainstream" smoke. Aging and dilution are provided prior to exposure to simulate constituent profiles similar to those described for human ETS exposure (Coggins *et al*., 1992). Few studies using exposures specifically designed to simulate human ETS exposure have as yet been published, however.

~~Tobacco-related Disease Research Program (TRDRP, 1992). *Grants awarded July 1992.*~~

~~Tobacco-related Disease Research Program (TRDRP, 1991). *Abstracts of Funded Research Projects 1989-1990 Funding Cycle*. University of California, Office of Health Affairs.~~

Add the following to section 1.3

1.3.4 Attributable risk

To provide a context for judging the importance of effects caused by ETS exposure, estimates of ETS-related morbidity and mortality are provided. The estimates are derived from data on prevalence and relative risk, through assessing the attributable fraction, also called the attributable risk (Breslow and Day, 1980; Kelsey et al., 1996). The attributable fraction is the maximum proportion of disease occurrence potentially eliminated if exposure were prevented. US EPA (1992) used an attributable fraction approach in estimating national figures for ETS-related respiratory health effects. In fact, the national figures derived by US EPA (1992) are used as the basis for deriving California-specific values for childhood asthma induction and exacerbation, bronchitis or pneumonia in young children, and lung cancer: the US estimate is multiplied by 12%, the fraction of the US population residing in the State. US statistics reported in the published literature for ETS-related heart disease mortality (Wells, 1988 and 1994; Steenland, 1992; Glantz and Parmley, 1991) are similarly used to estimate California-specific impacts. In this report, we calculate California-specific values for SIDS, low birth weight, and otitis media, using California prevalence data and relative risk values to first estimate the attributable fraction.

To the extent that smoking prevalence and ETS exposure have been declining in recent years and that California differs from the rest of the country, the California-specific values derived from US estimates may be overstated. However, cases of lung cancer occuring today are a consequence of ETS exposures over past decades, and since smoking prevalence in California has been near national levels until the mid-1980's, the differences noted should not significantly impact the accuracy of the California estimate. For heart disease mortality, this issue is more difficult to judge since the importance of current versus past exposures is not clearly understood.

Other sources of uncertainty in estimates based on the attributable fraction method include limited information on prevalence of current and past smokers and relative risks of disease associated with smoking status. Methods to describe the sensitivity of these factors to morbidity and mortality estimates derived using an attributable risk formulation have recently been discussed (Taylor and Tweedie, 1997).

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A "weight-of-evidence" approach has been used to describe the body of evidence on whether or not ETS exposure causes a particular effect. Under this approach, the number and quality of epidemiological studies, as well as other sources of data on biological plausibility, are considered in making a scientific judgment. Associations that are replicated in several studies of the same design or using different epidemiological approaches or consideringunder different sourcescircumstances of exposure are more likely to represent a causal relationship than isolated observations from single studies (IARC, 1996). If there are inconsistent results among investigations, possible reasons are sought (such as adequacy of sample size or control group, methods used to assess ETS exposure, range in levels of exposuredifferences in amount of exposure), and results of studies judged to be of high quality are given more weight than those of studies judged to be methodologically less sound. General considerations made in evaluating individual studies include study design, appropriateness of the study population, methods used to ascertain ETS exposure, as well analytic methods, such as the ability to account for other variables that may potentially confound the ETS effect (see, e.g., IARC, 1996). Increased risk with increasing levels of exposure to ETS is considered to be a strong indication of causality, although absence of a graded response is not necessarily evidence against a causal relationship (IARC, 1996).

Table 1.1
Use the same revised footnotes as provided for Table ES-2 (see above)

Revisions to Chapter 2

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This chapter provides background information on the prevalence and measurement of exposure to ETS, and emphasizes investigation and monitoring methods used in epidemiological evaluations of health effects. Section 2.2 briefly reviews the physical and chemical properties of ETS, and identifies some of the important biologically active constituents present in ETS. Section 2.3 discusses various techniques that have been used to measure ETS concentrations in indoor environments. Determination of ETS contamination is a challenge as ETS is a complex mixture of over 4,000 compounds and it is neither feasible nor practical to characterize every individual constituents of ETS. Given the complex nature of ETS, markers and tracers of ETS are measured to assess ETS exposures. The role and limitations of some ETS markers, such as nicotine, particulate matter in air, and polycyclic aromatic hydrocarbons, are discussed in this section. Section 2.4 addresses the use of biomarkers to measure ETS exposure. In addition to ETS concentration in air, the level of biomarker measured is also dependent on an individual's uptake, distribution, metabolism, and excretion of the chemical of interest. This section describes the use and limitations of some of the biomarkers, such as nicotine and cotinine in physiological fluids, in determining ETS exposure.

One problem with ETS markers and biomarkers is that most of them are only capable of estimating ETS exposure over a relatively short period of time, from a few hours to several weeks; whereas, many health effects of ETS are believed to be associated with long-term exposures that are measured in months if not years. In order to address this difficulty, most epidemiological studies cited in this ~~assessment~~ report used questionnaires or interviews to determine the status of the subjects regarding long-term exposure to ETS. Some studies also used measurements of ETS markers and biomarkers as supplemental information. And just like any epidemiological study that relies on questionnaire or interviews for exposure information, these studies are subjected to the problem of misclassification. Section 2.5 of this chapter describes some of the difficulties associated with classifying subjects into exposure categories based on the smoking status of other household members. As of today, no perfect method for quantifying ETS exposure has been found. Yet as demonstrated by many studies cited in the other chapters of the ~~assessment~~report, epidemiologists are able to use the information obtained from questionnaires or interviews in classifying the subjects into categorical groups of ETS exposure (*e.g.*, none, low, medium or high). The categorical exposure information is then used to evaluate health risks associated with ETS exposure. However, one drawback of this approach is that it decreases the sensitivity or power of a study, *i.e.*, it will not show a positive association when ETS exposure and a health effect is only moderately related to ETS exposure.

Though many ETS monitoring methods (e.g., nicotine and respirable suspended particulates in air, cotinine in body fluids) are discussed in the chapter, risk assessment on ETS exposure is seldom performed based on monitoring results. Some of the reasons include short sampling duration in most studies; large uncertainty in extrapolating the ETS levels measured at a specific location to the general population; and large uncertainty in estimating the exposure frequency and

exposure duration of the general population to ETS. Consistent with the approach used by the National Research Council (1986), U.S. EPA (1992), DiFranza (1996), and Wells (1994), this report uses prevalence assessment for the estimation of health risks that are associated with past or recent exposure to ETS. Epidemiologists often use prevalence assessment, which makes use of semi-quantitative exposure information such as job classification or duration of exposure, for the estimation of health risks associated with occupational and environmental hazards.

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Although many constituents present in mainstream and sidestream smoke are the same, there are important differences in the rates they are emitted into the air, due to physical and chemical differences in the burning conditions present during their generation ~~(see U.S. EPA, 1992: Section 3.2).~~ As discussed in the Respiratory Health Effects of Passive Smoking: Lung Cancer and Other Disorders (U.S. EPA, 1992: pages 3-2 to 3-10), ~~S~~some constituents have a higher rate of release into sidestream than mainstream smoke; while for others, the reverse is true. Once emitted into the air, sidestream smoke may undergo various physical and chemical changes. Dilution, chemical reactions, deposition and other removal processes may decrease the concentration of the airborne constituents of ETS, alter the size distribution of suspended particles, and chemically modify some of the more reactive constituents of ETS.

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(2.2.2.2 Toxicants with Carcinogenic Effects)

Over 50 compounds have been identified in tobacco smoke which are recognized as known or probable human carcinogens. These compounds, which may occur naturally in tobacco or which are formed during combustion, reside mainly in the particulate phase (IARC, 1986). Most of the major classes of carcinogens, including both organic and inorganic constituents, are represented. Table 2.2 lists those compounds detected in tobacco smoke for which there is some evidence of either animal or human carcinogenicity, as evaluated by the U.S. EPA or the IARC; also in Table 2.2 are compounds listed as carcinogens under California's Safe Drinking Water and Toxic Enforcement Act of 1986 (Proposition 65) (California Code of Regulations, Title 22, Section 12000), and tobacco smoke constituents that have been identified as Toxic Air Contaminants by the California Air Resources Board (ARB, 1993). Tobacco smoke itself is listed as a carcinogen under Proposition 65.

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(2.3.1 Introduction to Exposure Measurement)

This section summarizes a number of different techniques used by researchers for estimating the degree of ETS exposure of their subjects. In order to investigate the health effects of ETS exposure, epidemiologists characterize the exposure level of their subjects to determine the extent to which exposure is correlated with an adverse health effect. Given the extreme spatial and temporal variation of ETS concentration in indoor and outdoor environments, it is not feasible, technically and economically, to accurately determine the long-term ETS exposure history of an individual. Yet often times it is the long-term exposure to ETS that is of interest in

examining health effects, such as developmental effects and cancers. Epidemiologists circumvent this difficulty by using questionnaires or interviews to determine the status of the subjects regarding long-term exposure to ETS and then classifying the subjects into categorical groups of ETS exposure (*e.g.*, none, low, medium, or high). In this way, they make the best use of the ~~limited~~ semi-quantitative exposure information available without compromising the validity of the study results. One drawback of this approach is that it decreases the sensitivity or power of the study, *i.e.*, a study will not show a positive association when ETS exposure and an adverse health effect is only moderately, related. Some of the indirect and direct methods used by researchers in the study of ETS exposure are discussed in the following sections.

Indirect methods for assessing exposure include measurements of indoor air concentrations of ETS constituents (discussed in this section) and population surveys and questionnaires used to assess the characteristics, patterns and extent of exposure (Section 2.5). ~~Modeling exposure on the basis of measured or modeled air concentrations and the time an individual spends in a specific environment, another indirect method, is not discussed in this document.~~ Direct methods for assessing ETS exposure include the use of personal monitors (discussed in this section and in Section 2.4) and measurement of biomarkers of exposure. Personal monitors measure concentrations of ETS constituents at or near the breathing zone and can be worn by individuals to assess exposures occurring in a specific location or accumulated throughout the day, thus providing an integrated measure of short-term exposure. They are often used in conjunction with other methods to compare or validate assessment of exposure. Measurement of biomarkers, ETS constituents or their metabolites in physiological fluids (such as urine, serum, and saliva), is the most direct assessment of ETS exposure available (Section 2.4). They are often used to study exposure prevalence and evaluate the degree of misclassification in epidemiological studies.

The use of air models is another indirect method for assessing ETS exposure. Recently, some researches have developed and successfully applied models for predicting airborne ETS constituent concentrations (Ott *et al.*, 1992). For example, using the estimated cigarette source strength, air exchange rate and volume of the room, Klepeis *et al*. (1996) were able to predict minute-by-minute indoor time series and time-averaged respirable suspended particles concentrations from ETS. However, airborne ETS constituent concentrations derived from this type of model are location and situation specific and cannot be easily applied to the general population. Air models and human activity pattern models are not discussed in this document.

(2.3.2 Indoor Air Measurements of ETS)

Given the complex chemical composition of ETS, air concentrations are typically assessed by measuring individual ETS constituents, referred to as tracers, markers, or proxy compounds. Nicotine and respirable suspended particulates (RSP) are the most widely used markers for the presence and concentration of ETS in indoor environments. Recently, some researchers have used 3-ethenylpyridine, solanesol, and ultraviolet particulate matter as markers of ETS and suggested that they may be better correlated with other constituents of ETS than nicotine and RSP (Hodgson *et al*., 1996; Jenkins *et al*., 1996). ~~However, these markers have not been widely adopted by other researchers in the field, and have only been used in a limited way for measuring ETS concentrations in real world environments.~~

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Measurements taken in a wide variety of indoor environments in the U.S. indicate that most average concentrations of nicotine range about 100-fold, from 0.3 to 30 $\mu g/m^3$. The average concentration in residences with one or more smokers typically ranges from 2 to 10 $\mu g/m^3$, with high values of up to approximately 14 $\mu g/m^3$. Measured concentrations are typically higher in the winter than in summer months. In data collected from the mid 1970s through 1991, concentrations of nicotine in the workplace were similar to those measured in residences, with the range of average concentrations showing considerable overlap for the two locations. However, the maximum values for workplaces were considerably higher than in residences. In a recent paper, Hammond (1995) showed that ETS exposures in workplaces that allow smoking are comparable with and often greater than, the ETS exposures in smokers' homes. The highest nicotine concentrations in indoor environments were measured in bars and in the smoking sections of airplanes, with levels reaching as high as 50 to 75 $\mu g/m^3$ (U.S. EPA, 1992) (note: for several years, smoking has been prohibited on domestic flights of commercial airplanes). In a comprehensive survey of indoor measurements, the maximum nicotine concentrations were 30 $\mu g/m^3$ or less in over 50% of the studies examined, and less than 100 $\mu g/m^3$ in 90% of the studies (Guerin *et al.*, 1992). The highest reported level in the survey was 1010 $\mu g/m^3$, measured in a passenger car with the ventilation system shut off. In selected studies using controlled and field conditions, the concentrations of nicotine were found to increase as a function of the number of smokers present and the number of cigarettes consumed (U.S. EPA, 1992: Section 3.3.1.2 and ~~Figure 3-12a~~pages 3-32 to 3-33).

Results of four studies (three in the U.S.) using personal monitors to assess exposure of nonsmokers to nicotine are presented in U.S. EPA (1992: ~~Table 3-5~~page 3-37). The average personal exposures associated with the specific microenvironments in the U.S. for which measurements were taken ranged from 4.7 to 20.4 $\mu g/m^3$. In comparing the levels determined from stationary and personal samples, Guerin *et al.* (1992) reported that in one study, concentrations determined by the stationary sampler were higher than those from the personal monitor. In a second study, the reverse was found to be true. In a more recent study (Jenkins *et al*., 1996), breathing zone air samples of approximately one hundred nonsmoking individuals in each of 16 metropolitan areas of the United States were taken. The mean 24-hr time weighted average nicotine concentration for those who were exposed to ETS at work and away from work

(3.27 μg/m^3) is higher than those who were only exposed to ETS away from work (1.41 μg/m^3) or those who were only exposed at work (0.69 μg/m^3). The mean nicotine concentration measured by personal monitoring for those who were not exposed to ETS is 0.05 μg/m^3.

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Studies comparing RSP concentrations in similar locations in which smoking does and does not take place consistently show higher RSP concentrations in environments where smoking occurs. Typically, the differences range from less than 10% to approximately three-fold higher, although larger differences have been reported (Guerin *et al.,* 1992). Under selected and controlled field conditions, the concentration of ETS-associated RSP has been found to increase with increased smoking (U.S. EPA, 1992: ~~Figure 3-12b~~page 3-34).

Recently, Ott *et al*. (1996) measured RSP in a large sports tavern in Northern California on 26 dates between 1992 and 1994 during which smoking was allowed followed by additional measurements during the year after smoking was prohibited. Though the degree of active smoking in the tavern was characterized as low by the authors, they reported the average RSP concentration was 56.8 μg/m^3 above the outdoor concentrations. Between 1994 and 1995, after smoking was prohibited, another set of 26 follow-up visits (matched by time of day, day of the week, and season to the earlier smoking visits) yielded an average concentration of 12.9 μg/m^3 above the outdoor levels, or an overall decrease in the average RSP concentration of 77% compared with the smoking period. No decrease in tavern attendance was evident after smoking was prohibited.

Results of five studies using personal monitors to assess exposure of nonsmokers to RSP are presented in U.S. EPA (1992: ~~Table 3-6~~page 3-38). Only three studies reported exposures integrated over several different environments, with exposure to ETS-associated RSP resulting in increased concentrations of 18 to 64 μg/m^3. Those individuals reporting exposure to ETS had substantially increased exposure to RSP as compared to individuals reporting no ETS exposure. In a more recent study, ~~(~~Jenkins *et al*., (1996) took breathing zone air samples of approximately one hundred nonsmoking individuals in each of 16 metropolitan areas of the United States. The mean 24-hr time weighted average RSP concentration for those who were exposed to ETS at work and away from work (47 μg/m^3) is higher than those who were only exposed to ETS away from work (33 μg/m^3) or those who were only exposed at work (28.7 μg/m^3). The mean RSP concentration measured by personal monitoring for those who were not exposed to ETS is 18.1 μg/m^3.

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(2.3.5.2 Other Organic Compounds)

Other toxic air pollutants (30 volatile and semivolatile organic compounds) were measured in a study of 128 homes in the city of Woodland. Indoor samples were collected in all homes and personal monitoring samples for volatile organic compounds were collected for 93 individuals. About 61% of the homes were non-smoking homes, and smoking occurred in about 39% of the homes during the monitoring period. Homes (n=15) in which heavy smoking (>20 cigarettes smoked/ 24-hour period) occurred had elevated concentrations of benzene, para-dichlorobenzene, tetrachloroethylene, trichlorethylene, and xylene (ortho and meta/para) as compared to homes with no smoking. Personal monitoring air concentration samples of benzene and para-dichlorobenzene were also higher for persons in homes with “any smoking” and those with "heavy smoking" compared to homes with no smoking. However, for both the indoor and personal air measurements, these differences were not statistically significant at the $p = 0.05$ level, as determined using pairwise t-tests (Sheldon *et al.*, 1992a).
Hodgson *et al*. (1996) using 3-ethenylpyridine as a tracer, investigated the contribution of ETS to the measured volatile organic compounds in several smoking areas in California. They reported ETS was estimated to contribute 57-84% of the formaldehyde concentrations, 43-69% of the 2-butanone concentrations, 37-58% of the benzene concentrations, and 20-70% of the styrene concentrations. The fractional contributions of ETS to the concentrations of acetone, toluene, ethylbenzene, xylene isomers, and d-limonene were all less than 50%.

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(2.4.2 Biomarkers: Nicotine and Cotinine)

(2.4.2.1 Nicotine and Cotinine: General methodological issues)

Nicotine and cotinine, a major metabolite of nicotine, are the most widely used biomarkers of ETS exposure. In general, the presence of nicotine or its metabolites in physiological fluids can be attributed to exposure to tobacco smoke. The few exceptions include occupational exposure to tobacco leaves (Gehlback *et al.*, 1975) and nicotine products, use of smokeless tobacco products, chewing of nicotine gum, and use of nicotine patches or other aids for smoking cessation. Low levels of nicotine have been found in tea and in edible solanaceous plants including eggplant, green pepper, and tomato (Castro and Monji, 1986; Sheen,1988; Davis *et al.*, 1991; Domino *et al.*, 1993a,b). While some authors have claimed that dietary intake of nicotine may be of practical importance in the use of nicotine and cotinine as biomarkers of ETS exposure (Domino *et al.*, 1993a,b), others dispute this assertion (Benowitz, 1996; Henningfield, 1993; Jarvis, 1994; Pirkle *et al*., 1996; Repace, 1994). In general, the levels of nicotine and its metabolites in physiological fluids resulting from the ingestion of foods has not been found to significantly impact the levels resulting from exposure to nicotine from tobacco sources.

As biomarkers of exposure, nicotine and/or cotinine are typically measured in blood, saliva, or urine. For studies requiring a quantitative assessment of exposure, blood has been recommended as the fluid of choice, although saliva and urine are also considered acceptable (Watts *et al.*,

1990). Cotinine levels in saliva and plasma tend to be similar, whereas the ratio of urinary to plasma levels is generally a factor of 5 to 6 (~~*e.g.*,~~ Repace and Lowrey, 1993; Benowitz, 1996).

Urinary cotinine excretion is variable across and within individuals, depending on renal function, urinary flow rate, and urinary pH (Benowitz, 1983). Urinary results may be expressed as nanograms of cotinine per milligram of creatinine in order to correct, in part, for differences in dilution effects. Because the amount of endogenous creatinine produced is a function of muscle mass, and hence, age and sex, interindividual excretion rates of creatinine are also variable. In particular, cotinine:creatinine ratios may not be appropriate for comparisons between males and females. In addition, low levels of creatinine in infants relative to adults may result in cotinine to creatinine ratios for infants that fall into the range reported for active smokers (Watts *et al.*, 1990). In general, it is preferable to collect urine over 24 hours, although is impracticable for most studies.

The ~~biological~~average half-life of cotinine in ~~nonsmokers~~ different body fluids (plasma, saliva and urine) is about the same, approximately ~~one to two days~~ 15-19 hours (~~Sepkovic *et al.*, 1986; Hoffman *et al.*, 1987; Haley *et al.*, 1988~~Benowitz *et al.*, 1994; Jarvis *et al.*, 1988), making it a good indicator of the integrated ETS exposure over the previous two to three days. The half-life is typically longer in infants and children, averaging approximately 65 hours in neonates, 60 hours in infants under 18 months, and 40 hours in children over 18 months (~~see~~ U.S. EPA, 1992: ~~Figure 3-14~~page 3-41). Nicotine, with its shorter half-life of approximately two hours, is a good indicator of exposures occurring within the previous few hours.

An interlaboratory study of data from 11 laboratories in six countries was conducted to compare analytical results for nicotine and cotinine in serum and urine (Biber *et al.*, 1987). The results of the study indicate that both gas chromatography (GC) and radioimmunoassay (RIA) techniques reliably quantitate nicotine and cotinine in urine and serum samples and that both techniques are capable of discriminating between smokers and nonsmokers. However, interlaboratory variability was high. While the coefficient of variation for spiked samples was low (9-13%), the coefficient of variation for samples from smokers was fairly large, ranging from 18% to 45% for serum and from 21% to 59% for urine. In addition, cotinine levels reported for urine, as determined by RIA, were about 60% higher than the levels determined by GC. Besides cotinine, some less specific immunoassays can also react with other metabolites of nicotine. Cotinine levels reported for nonsmokers were extremely variable, and a number of laboratories could not detect cotinine in serum from exposed nonsmokers. Because of these various factors, caution should be used in making quantitative comparisons across studies. However, limitations in the design of this study have been noted (Watts *et al.*, 1990); additional studies are required to assess the comparability of these two assay methods and the results from different laboratories, as well as the performance of other methods (*e.g.*, high pressure liquid chromatography (HPLC)).

(2.4.2.2 Nicotine and Cotinine: Measured Concentrations in Physiological Fluids of Adults)

A large number of studies are available which report concentrations of cotinine in physiological fluids of smokers and nonsmokers. The levels of ETS encountered by exposed nonsmokers during their daily activities are sufficiently high that nicotine and cotinine are detected in their

urine, blood, and saliva. The physiological concentrations of cotinine detected in saliva and plasma of nonsmokers typically range from 0.5 ng/ml to 10 or 15 ng/ml (Guerin *et al.*, 1992; U.S. EPA, 1992), and urinary concentrations range to 50 or more ng/mL. For example, Cummings *et al.* (1990) reported that a population of 663 self-reported nonsmokers attending a cancer-screening clinic in New York had a mean urinary cotinine concentration of 8.84 ng/ml (range: 0 to 85 ng/ml) (in the Cummings *et al.* study, a cutoff level of 90 ng/ml was used to distinguish between smokers and nonsmokers). In a population-based study of Hispanics in New Mexico, mean salivary concentrations of cotinine in various age groups ranged from 0 (not detected) to 6.0 ng/ml (Coultas *et al.*, 1987). The studies by Coultas *et al.* (1987) and Cummings *et al.* (1990) are described in Section 2.6.3. However, it is important to realize that some of the differences in cotinine levels reported here could be explained by the different analytical methods used. For example, cross-reactivities of cotinine immunoassays with trans-hydroxycotinine and/or cotinine glucuronide is probably an important contributor to the often significantly higher levels of urinary cotinine measured by this method compared to those measured by GC. Thus, in comparing cotinine levels reported in various studies, it is important to consider the analytical method employed and what are the analytes that were being measured.

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(2.4.2.3 Nicotine and Cotinine: Comparison of Levels in Smokers, and ETS-exposed and Unexposed Nonsmokers)

Studies comparing ETS-exposed and unexposed nonsmokers and active smokers (Matsukura *et al.*, 1979; Wilcox *et al.*, 1979; Williams *et al.*, 1979; Haley *et al.*, 1983; Hill *et al.*, 1983; Jarvis and Russell, 1984; Wall *et al.*, 1988) have consistently found that measurement of cotinine in the urine, saliva, or serum can distinguish active smokers from unexposed and ETS-exposed nonsmokers. Findings have been less consistent with regard to the use of such assays to distinguish between self-reported unexposed and ETS-exposed nonsmokers. As discussed by Wall *et al.* (1988), potential reasons for this include intersubject variability in nicotine metabolism (Benowitz *et al.*, 1982); time of day of sample collection (Jarvis and Russell, 1984); misreporting of smoking status (Jarvis and Russell, 1984; Jarvis *et al.*, 1987); misreporting of non-smoking status; adjustment of cigarette consumption for nicotine content (Benowitz *et al.*, 1983); and over- or underreporting of ETS exposure. Another reason is that in the past some of the methods used for cotinine analysis are simply not sensitive enough to detect the very low concentration of cotinine in saliva or serum resulting from of ETS exposure.

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(2.5 Exposure Measurement: Use of Questionnaires)

Epidemiological studies typically evaluate exposure to ETS using questionnaires in which the subject reports his or her own exposure history and smoking status. In studies using questionnaires alone to assess ETS exposure, misclassification of true exposure status can result from a number of factors, including: limited questions (*e.g.*, spousal smoking status only); possible deception in reporting spousal smoking status; or inadequate recall of exposure (*e.g.*, parental smoking status; lack of awareness of contemporary exposure). ~~In addition, misclassification of smoking status may occur when classification is based on self-report~~. Many studies cited in this report are aware of misclassification error and have taken appropriate steps to minimize its impact or adjusted the results to account for this source of error. This section summarizes the results of a number of studies that have examined the reliability and validity of information collected using questionnaires regarding ETS exposure and smoking status.

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Figures 2.3 and 2.4 show the percent of nonsmokers in California reporting exposure to ETS and the average daily duration as determined in this study. Of adult nonsmokers, 43% reported exposure to ETS, as did 64% of nonsmoking adolescents (Jenkins *et al.*, 1992). For smokers and nonsmokers combined, approximately 61% of adults and 70% of adolescents (age 12 through 17) reported exposure to ETS at some time during the day (at the time of the survey, 22.5% of the population reported active smoking on a given day). The groups with the lowest percent reporting exposure were children and infants and preschoolers, ranging from 35% to 45%, as a function of age and sex. About 38% of children under age 12, statewide, were exposed to ETS at some time during a typical day. ~~However, a~~Among those infants and preschoolers who were exposed to ETS, the average duration of their exposure was as long as that of adults (about four hours); children aged 6-11 years who were exposed had an average exposure duration of three hours (Lum, 1994a,b, personal communication).p. 3-15

Chen and Pettiti (1995)

Chen and Pettiti conducted a case-control study of IUGR among singleton, term infants born in 1991 in Contra Costa County, California. Controls were non-growth retarded, non-malformed infants identified from birth certificates. ETS exposure was ascertained by first asking about location (work, home, car, other) and then the total number of hours per week exposed to ETS for each trimester. The small sample of non-smokers is a major limitation of the study, as well as the fairly low completion rate (50-55%). ~~In addition, a number of known risk factors for IUGR were not identifiable as such in this study, including infant gender, maternal weight gain and prenatal care, as well as alcohol use.~~ By quintiles of average hours of exposure over all trimesters, there was no indication of an increased risk of term IUGR with greater exposure. Most women reported exposure in “other” places, but none of the locations considered showed

evidence of increased risk of term IUGR. Adjusting for a variety of variables showed a decreased risk with exposure but very wide confidence intervals with home exposure or home and elsewhere (ORs about 0.5); work and car exposure had odds ratios around one. In addition to low power and a fairly high refusal rate, this study may be hampered by recall error, although subjects were interviewed fairly soon after delivery (mean was eight months).

Roquer et al. (1995)

Roquer *et al.* (1995) conducted a small study of Spanish women presenting for labor and interviewed them after delivery. ETS exposure was defined as "significant" if the woman was exposed to the smoke of 20 or more cigarettes per day at work or home; that is, exposure to one smoker who smoked a pack or more per day or two smokers who each smoked a half-pack per day. A major problem with the design is that the interviewer measured the infant within four hours after birth, so outcome determination was not blinded with respect to exposure. The mean birthweight of infants whose mothers were exposed was 192 grams less than that of infants whose mothers were unexposed, and was comparable to the weight decrement in infants of women who smoked 1 to 9 cigarettes per day. Infants of mothers who smoked heavily had weight decrements of over 450 grams. No confounders were considered, but parity and employment status were similar in ETS-exposed and unexposed women. The rate of IUGR was about doubled with ETS exposure, again similar to that seen in infants of light smokers, but was not statistically significant (Table 3.3). ETS exposure was associated with a reduction of one centimeter in length (calculated 95% C.I.=-1.8,-0.2)~~p< 0.001~~). This study is limited by its small size and lack of adjustment for confounders, as well as by the possible measurement bias (although weight is subject to less measurement error than length).

Revisions to Chapter 3

Page 3-7

Zhang and Ratcliffe (1993)

Zhang and Ratcliffe (1993) examined the effects of paternal smoking on livebirths who had served as controls in a study of birth defects. Among singleton term births of nonsmoking women in Shanghai, there was a crude weight decrement of 26 grams associated with paternal smoking. Adjustment for parity, maternal age, gestational age and mother's occupation by multiple linear regression yielded a decrement of 30 grams (95% CI= -66 to 7). There was a non-linear ~~dose-response~~ trend by amount smoked, with greater adjusted weight decrements seen up to 19 cigarettes/day, but an increase in weight at higher levels (20 or more cigarettes/day) (Table 3.1). The confidence interval at the higher level of paternal cigarette consumption overlapped with the decrements estimated at lower smoking levels. The non-monotonic trend in dose-response may be due to chance, or inaccuracy in reporting of paternal amount by their spouses, or a confounding variable not taken into account. The paternal smoking ascertained appeared to reflect usual smoking status, not necessarily that during pregnancy.

Martinez et al. (1994)

Martinez *et al.* (1994) studied enrollees of the Tucson Children's Respiratory Study, conducted in a large health maintenance organization in Tucson, Arizona. Information (including birthweight) was obtained by nurses while the mothers were in the hospital following the birth. Each parent was given a questionnaire to answer about his or her own smoking habits, and the person's current smoking habit was used to estimate the amount smoked during pregnancy, because it was obtained so soon after delivery. Among the 992 non-smoking mothers, infant birthweight significantly decreased with increasing paternal smoking; infants whose fathers smoked more than 20 cigarettes per day had a mean weight decrement of 88 grams. Maternal smoking of more than 20 cigarettes per day was associated with an average 273~~250~~ gram decrement. In a multiple regression analysis adjusting for gestational age, gender, race, parity, education, and maternal age, paternal smoking was associated with a 34 gram decrement for approximately each additional 10 cigarettes smoked per day (coded as an ordinal variable: 0=none, 1=1-10, 2=11-20 and 3=>20 cigarettes/day) (Table 3.1). Duration of pregnancy was not affected by the smoking habit of either parent. Cotinine measured in cord blood for a sub-sample indicated that perhaps 1.5% of the women were smokers misclassified as non-smokers. The two women thus misclassified had non-smoking spouses, so it is not clear that such misclassification would necessarily lead to finding a greater weight decrement with ETS exposure, which is a common criticism of studies of ETS. Detection of cord blood cotinine was reported to be strongly correlated with the number of cigarettes smoked by the father. Minor limitations of this study are the lack of information on other potential confounders, such as alcohol consumption, and the use of smoking habits reported after delivery to represent smoking during pregnancy; however, it is unlikely that women who smoked during pregnancy would quit after delivery.

Page 3-19

Rebagliato et al. (1995a)

As noted in Section 3.2.2.2, Rebagliato *et al.* (1995a) studied ETS exposure in 710 nonsmoking women using a questionnaire and sampling saliva for cotinine. The investigators examined birthweight by quintiles of cotinine levels less than 14 ng/ml, with subjects having cotinine levels of 0 to 0.5 ng/ml serving as the reference group. In the highest quintile (>1.7 ng/ml), there was a crude weight decrement of 98 grams, which was reduced slightly to 87 grams after adjustment for covariates (Table 3.4). There was little evidence for a dose-response trend as subjects in the fourth quintile had a slight weight increment, but the highest category examined does not represent a particularly high ETS exposure level. For comparison to Haddow *et al.* (1988), the weight decrement associated with any cotinine level greater than 0.5 ng/ml was 35 grams. The adjusted weight decrement found with high cotinine level was greater than that found with high self-reported exposure. However, in a separate analysis of exposure measures (Rebagliato *et al.*, 1995b), the authors reported that duration of recent exposure to each source of ETS (as self-reported) and the summary measure at all locations were significantly correlated with cotinine levels (Spearman's $r = 0.52$ for all locations). The apparent inconsistency may be due to differences in the way women report their own exposure, so that some misclassification results.

Page 3-14

Mainous and Hueston (1994)

Mainous and Hueston (1994) analysed data from the 1988 National Health Interview Survey (NHIS), a household interview conducted on a nationwide sample, examining pregnancies occurring in the past six years (mean was two years). ETS exposure was determined by asking respondents to categorize their contact with smokers (friends, co-workers or family members) as "occasional, often, always, or never" during pregnancy. There was little difference in the frequency of LBW infants among ETS exposed versus unexposed women. However, when examined by categories of increasing exposure, there was a trend towards increasing rates of LBW ($p < 0.01$). Controlling for race, parity, income and maternal age, the adjusted odds ratio was about 1.6 for the highest exposure category (Table 3.3) and was greater among non-whites (OR=2.3, 95% CI=1.1 - 5.0). Comparing mean birthweight, women in the highest exposure category had infants that weighed on average 84 grams less than ~~unexposed~~ infants in the very low exposure category (Table 3.3). No dose-response trend in mean birthweight was noted for lower levels, which the authors interpreted as evidence for a threshold effect. The weight decrements were unadjusted and information was not included about other potential confounders of the relationship with LBW. Further, this study may be subject to some recall error, as pregnancies could have occurred up to six years earlier and the measure of outcome (as well as exposure) was obtained from the women themselves. The qualitative measure of exposure used may be less subject to recall error than a more quantitative measure would have been. The main advantage of the study is its large, population-based sample.

Page 3-15

Rebagliato et al. (1995a)

In the best of the new studies, Rebagliato *et al.* (1995a) conducted a prospective cohort study (also in Spain) of non-smoking pregnant women. Subjects were interviewed in their third trimester of pregnancy and a saliva sample was collected for cotinine analysis. The investigators asked extensive questions about exposure from four sources and on different days of the week to calculate an average weekly exposure during pregnancy. Of the 710 nonsmoking women, 88% reported some exposure; their infants were on average 85 grams lighter than those of unexposed nonsmokers. However, no dose-response trend was evident and results were not consistent by source, with exposure at home not resulting in a birthweight decrement. In a multiple regression model which adjusted for a number of covariates including gestational age (but not alcohol use), the highest exposure category was associated with a 41 gram decrement in birthweight (Table 3.3), while other categories had decrements ranging from 26 to 77 grams. Because of the small numbers of subjects in these categories, none of the weight decrements were statistically significant. More women were exposed at home, and for longer periods of time, so the inconsistent results are difficult to explain. However, exposures at work may be more intense, with more smokers present.

Page 3-23

Lending further support in terms of a biological basis for these findings from epidemiologic and animal studies are the well-established relationships, first, between active smoking and fetal growth retardation in humans, and second, between constituents of tobacco smoke (e.g., nicotine, carbon monoxide, toluene, cadmium) and fetal growth retardation in animals. There appears to be sufficient evidence that ETS is associated with a decrement in birthweight (and fetal growth retardation), based on all sources of data with primary emphasis on the high quality epidemiologic studies. The effect is of a small magnitude (perhaps 25-50 grams) that may not be clinically significant for an individual infant at low risk. Yet, if the entire birthweight distribution is shifted lower with ETS exposure, as it appears to be with active smoking, infants who are already compromised may be pushed into even higher risk categories. Low birthweight is associated with many well-recognized problems for infants and with perinatal mortality. ~~A meta-analysis of studies conducted up to mid-1994 reported a weighted average of a 28 gram decrement in mean birthweight (95% CI= -40 to -16), a summary odds ratio of 1.2 (95% CI= 1.1 1.3) for IUGR or LBW at term and 1.4 (95% CI=1.1 1.8) for LBW (Windham *et al.*, 1995a). An increased risk of 20-40% in LBW with ETS exposure would affect a large number of infants in California. Assuming relative risk estimates of 1.2 to 1.4, a rough estimate of the number the ETS-related low birthweight newborns in California is 1,200 to 2,200.~~ A meta-analysis of studies conducted up to mid-1994 was reported (Windham *et al.*, 1995a), which pooled results of the studies into a summary estimate based on a weighted average (with the weight equal to the square of the inverse of the standard error of the estimate of each study, as in Greenland, 1987). Studies which did not provide an error measurement (or confidence interval) could not be included in the summary. If study results appeared heterogeneous (p-value for homogeneity chi-square > 0.10), and influence analysis was conducted by removing studies individually to see which had the greatest effect on the results. The weighted average for difference in mean

birthweight was -28 grams (95% CI=-40 to -16) among studies limited to non-smoking women (e.g. with and without ETS exposure, n=12). The summary odds ratio for low birthweight at term or IUGR studies was 1.2 (95% CI=1.1-1.3)(n=8) and for LBW was 1.4 (95% CI=1.1-1.8)(n=4). The latter excludes the Underwood *et al.*(1967) study, which appeared to be an outlier but had a large influence due to its high sample size, and had numerous methodological limitations as described earlier.

Page 3-31

Holmberg and Nurminen (1980)

A case-control study of central nervous system defects designed to examine occupational factors (Holmberg and Nurminen, 1980) also reported on parental smoking. Cases were identified from the Finnish Register of Congenital Malformations for the years 1976-1978 and controls comprised the live birth immediately preceding the case born in the same district. A questionnaire was administered to mothers of cases and controls within a few months of delivery. Based on a matched analysis, we calculated an odds ratio of 1.3 (95% CI= 0.74 - 2.5) for paternal smoking, restricted in the interview to "the time when the woman became pregnant". Maternal smoking showed a greater association (OR=2.1, 95% CI= 1.0 - 4.4), but the authors reported that this association was diminished when adjusted for solvent exposure. No confounders were considered in the analysis of paternal smoking, including maternal smoking.~~.~~

Page 3-34

None of the studies currently published had information on ETS exposure from multiple sources (*e.g.*, home and work), nor did any include measurement of a biomarker. Thus, an association will be more difficult to detect if there is misclassified exposure such that the comparison group includes pregnancies exposed to ETS from sources other than the spouse. Given that the results of studies of active smoking have been inconsistent, a teratogenic effect of ETS is unlikely to be strong; it would be very difficult to detect a significant association of a weak teratogen which occurs at such low levels with outcomes as rare as specific birth defects. Furthermore, because of the relative dearth of information on causes of malformations, it is difficult to determine whether confounding variables have been adequately controlled. Several of the studies did not exclude maternal smokers and only one of those adjusted for maternal smoking (Savitz et al., 1991).

Page 3-52

Rajini P, Last JA, Pinkerton KE, Hendrickx AG, Witschi H (1994). Decreased fetal weights in rats exposed to sidestream cigarette smoke. *Fund Appl Tox* **22**: ~~2~~4400-404.

Changes to Table 3.3

Study		Results[2]	
Authors (year) Country(study size [1])	**ETS Level (% Exposed)**	**Difference in Mean Weight**	**IUGR/LBW OR (95% CI)**
Ahlborg & Bodin (1991) Sweden (n=2,461 employed)	Home exposure only (16%)	-34 g (-82, 15) ~~(very small numbers)~~	0.7 (0.21-2.3) LBW (based on 3 affected infants)
Fortier *et al.* (1994)3	Home only (13%)		0.98 (0.67- 1.44) IUGR
Rebagliato *et al.* (1995a) Spain (n=710) Interview in 3rd trimester	Assessed hours per week from 4 sources Any exposure (88%) ≥42 hours/week (22%)	Any: -85g, crude any ≥42 hours/wk: -41g (-144, 61)[2] spouse ≥42hrs/wk: 31g (-103, 165)	- -

1 The study size (n) presented is for term births to nonsmokers, not the total study size.

2 Effect measure adjusted for a number of confounders, unless otherwise indicated as "crude". Abbreviations: LBW - low birth weight; IUGR - intrauterine growth retardation.

3 The analysis adjusted for LBW in previous births. This may result in substantial under estimation of effect.

Changes to Table 3.4

Study			Results	
Authors (year) Location	**Design (size)**	**Biomarker Levels[1]**	**Weight Difference**	**Low Birth Weight**
Rebagliato *et al.* (1995a) Spain	Saliva in 3rd trimester (n=710 nonsmokers)	≤ 0.5 = unexposed Quintiles of cotinine (Mean in ETS exposed = 1.2 ng/ml)	Any: -35g, crude Highest quintile (>1.7ng/ml): -87g, (adj.) (-174, -1)	- -

[1] Abbreviations: SCN = thiocyanate, CI = confidence interval, OR = odds ratio, r = correlation coefficient.

Changes to Table 3.6

Authors (yr) Location	Design (study size)	Exposure Definition[1]	Results	Comments
Mau & Netter (1974)[2] Germany	Interview in early pregnancy (n = 5,183)	Paternal smoking by amount (>10/day)	RR for severe BD = 2.6 (1.5-4.7) RR for facial clefts = 7.0 (p<.05) Cardiac defects = 1.9 (n.s.) NTDs = 1.7 (n.s.)	Looked at some confounders, but not adjusted. Little information on methods. (Appears to include maternal smokers).
Seidman *et al.* (1990)[2] Israel	Interview post-partum (n = 17,152 infants)	Paternal smoking (amount)	RR = 1.45 (0.73 - 2.8) for >30 cigs/day[2] and major BDs. RR = 1.1 (0.85, 1.5) for minor BDs.	Multivariate adjustment (results not shown). Little dose-response. ~~Effect of maternal smoking seen in older women only.~~

1 Among non-smoking women unless otherwise specified. Exposure ascertained from mother unless otherwise specified.

2 Confidence interval calculated by reviewer.
Abbreviations: BD = birth defects, NTD = neural tube defects, CNS = central nervous system, VSD = ventricular septal defect, CLP = cleft lip and/or cleft palate, CP = cleft palate, n.s. = not significant or p > 0.05.

Revisions to Chapter 6, Respiratory Health Effects

Page 6-6

Insert before the first full paragraph

Strachan and Carey (1995) reported the results of case-control study of residential environmental determinants of severe asthma among 763 children, aged 11-16, in Sheffield, England. To be eligible, the child must have had 12 or more episodes of wheezing or at least one speech-limiting attack of wheezing (during which the child could say only one or two words between breaths). Controls who had no history of asthma or wheeze at any age were frequency matched on age and school class. ETS exposure was assessed by parental questionnaire. The analysis focused on factors in the home environment that contributed to status as a case, which was defined as having had at least 12 episodes of wheeze, one or more speech-limiting attacks, or both. The only ETS-related data pertained to three current parental smoking categories: none, 1-10 or > 10 cigarettes/day. While paternal smoking was unrelated to the outcomes examined, maternal smoking >10 cigarettes/day was significantly related to the combined category of frequent wheezing plus speech-limiting attacks (crude odds ratio 2.28, $p<0.05$). However, in models adjusting for numerous other household factors (e.g., current and past pet ownership, type of pillow and bedding used, age of mattress, and so forth), the odds ratio for maternal current smoking was still elevated (1.49) but no longer significant. It is not clear from this report whether the investigators examined the "healthy passive smoker effect," i.e., whether the parents of children most severely affected stopped smoking because of the children's asthma. This study examines risk factors for having severe asthma versus not having asthma at all: it does *not* address whether exposure to ETS or other factors influence the severity of asthma among children who already have this disease.

Insert before the last paragraph

Bailey *et al*. (1994) report a primarily descriptive examination of patients served by the Comprehensive Asthma Program of the University of Alabama at Birmingham. Though the investigators apparently examined the prevalence of passive smoking among the 263 of 479 patients served by this clinic program, there were no data on ETS exposure assessment or prevalence or on the relationship of ETS exposure to asthma severity provided in the report, other than that the investigators "found no relationship between asthma severity and … passive smoking," and that "exposure at work was more common (for those who worked) than exposure at home." This report analyzed numerous asthma co-morbidities and potential determinants of severity and asthma management, but, unlike the Jindal study, provides no information about ETS exposure assessment, and hence is difficult to evaluate.

Hong *et al*. (1994) examined the influence of numerous lifestyle and behavioral influences on indices of asthma morbidity in 787 of 1352 eligible adult patients, aged 21-54, attending government-run asthma outpatient clinics in Singapore. Asthma morbidity was assessed by questionnaire and the dichotomous outcome variable of "increased morbidity" was designated to include, during the year preceding administration of the questionnaire, $\geq$ 1 "attack"/week (in the day or at night), $\geq$ 4 urgent care visits for asthma, $\geq$ 1 hospital admission, or $\geq$ 7 days of sick leave. Unlike the Jindal study, which undertook a quantitative assessment of the relationship between ETS exposure and a variety of indices of asthma severity, Hong *et al*. apparently collapsed their indices of severity into a single dichotomous variable, thereby decreasing substantially the likelihood of detecting any effect of ETS exposure. In addition, this study provides no detail about exposure assessment, other than that it was ascertained by questionnaire and that it was treated as a dichotomous variable. Dichotomizing ETS exposure as well would tend to bias the analysis towards the null hypothesis of no effect. These limitations, in addition to potential selection bias (fewer than 65% of eligible patients were included in the analysis) all limit the interpretability and generalizability of this study.

Change the second to last sentence on page 6-6 to:

"The results of one controlled chamber investigation suggest that even single exposures of adult asthmatics to ETS can elicit prolonged airway hyperresponsiveness (AHR), which could provide experimental support for the epidemiological observations."

Page 6-9
Insert before the last sentence of the first paragraph:

"In contrast, the use of ETS concentrations that exceed those likely to occur in most common exposure situations would tend to have the opposite effect (See Table 6-2)."

Section 6.2

A table of studies that were excluded after being identified as potentially relevant in the ETS/childhood asthma meta-analysis is being included.

Page 6-33

The second sentence of the last paragraph on the page has been changed to read:

The pooled RR for those studies with clinically diagnosed asthma as the outcome was1.44 (95% C.I. = 1.27-1.64) and did not significantly differ from that of studies examining "wheezy bronchitis or chronic wheeze/whistling in the chest" (pooled RR = 1.47, 95% C.I. = 1.34-1.61).

Page 6-34
Add after the first paragraph:

"Though the meta-analysis was not restricted to studies examining only maternal exposure, OEHHA compared the pooled estimates for asthma RRs for studies in which there were separate estimates for maternal smoking versus those for general household smoking. When exposure was related to maternal smoking the pooled RR was 1.60 (95% C.I. = 1.29-1.99), while that for household smoking generally was 1.34 (95% C.I. = 1.11-1.61)."

Add after the current second paragraph:

OEHHA staff also undertook an influence analysis, in which one study was dropped at a time and the pooled RRs were re-estimated. No single study (including all of those listed by the commenter) had a significant effect on the pooled estimates.

Modify the current third paragraph to read:

Most studies relied on crude measures of ETS exposure, i.e., parental reporting of the presence of household smokers or the estimated number of cigarettetes smoked in the home. Four studies, however, reported risk ratios in relation to exposure assessed by measurement of salivary or urinary cotinine as well as by parental reporting (Clark et al. 1993, Duff et al. 1993, Ehrlich et al. 1992 and Willers et al. 1991). In all four, the estimates risk ratios associated with exposure to ETS were higher when exposure classification was based on cotinine levels rather than on parental reporting, and produced a pooled RR of 2.52 (95% C.I. = 1.61-3.95). Because this estimate was based on only four studies, it combined the outcome categories of wheeze and clinical asthma.

Modify the fourth sentence of the last paragraph on p 6-34, as follows:

"As can be seen in Figures 6.1 and 6.2, most of the estimates of relative risk extracted from the investigations were statistically significant. Of the 37 studies included in the meta-analysis, 14 had point estimates greater than 2.0, suggesting a strong association between ETS exposure and the
occurrence of childhood asthma ("strength of association")."

Replace the last sentence of the last paragraph with:

"Recognizing the heterogeneity indicated during the process of creating pooled estimates in the meta-analysis, almost all studies had point estimates of relative risk significantly greater than one, and most were
statistically significant, whether the outcome was clinically diagnosed asthma or wheezy bronchitis. If there were no relationship between ETS and childhood asthma, one would expect a random distribution of point estimates above and below the null value. This

consistency is apparent despite the diversity of study designs and populations ("consistency")."

Page 6-36
Insert after the first paragraph:

Though not typically considered part of the Bradford Hill criteria, the potential role of confounding should also be considered in causal inference. In epidemiological studies, a confounder is a factor or variable that is associated with both the disease outcome and with the exposure of interest, and can produce a distortion of the relationship (or lack thereof) between the exposure and the disease outcome. The effect of a potential confounding variable can be addressed in the design phase of a study, or if data on the putative confounder are collected during the study, then the potentially distorting effects of the confounder can be controlled for statistically during the analysis. In any given study, there are likely to be few potentially confounding exposures sufficiently important to control for. For studies examining the relationship between childhood asthma and ETS exposure, probably the most important variables to be evaluated as potential confounders, given the current state of knowledge, include the child's age, history of atopy or allergy, parental history of asthma, allergy or other respiratory symptoms, and an indicator of family socioeconomic status, while other variables that ideally should be examined and adjusted for, if necessary, would include the child's gender, whether the child was breast-fed in infancy, type of fuel used for heating and cooking, the presence of allergens recognized to be risk factors for induction of asthma (e.g., from household pets or dust mites), home dampness and/or mold, serious lower respiratory infection in early childhood, number of siblings, and maternal smoking during pregnancy (to the extent that this can be segregated from post-natal exposure). Approximately 2/3 of the studies included in the meta-analysis controlled for three or more potential confounders and effect modifiers, and these studies tended to have greater estimates of relative risk of asthma than those studies that adjusted for fewer than three covariates. The association of ETS exposure with asthma was usually found to be independent of these various risk factors. Several studies examined or adjusted for ten or more potential confounders, and some adjusted for many more, e.g., Infante-Rivarde (1993) apparently adjusted for nearly two dozen variables, reporting an odds ratio of 2.77 (95% C.I. = 1.35-5.66) for maternal smoking of at least one pack of cigarettes/day. Nevertheless, routine adjustment for a long list of putative confounders is methodologically undesirable as it may affect the precision and therefore the significance of the estimate of the relationship between ETS exposure and disease.

Modify the fifth sentence of the second full paragraph, regarding the study by Cook et al. (1993), as follows:

"...several indices of lung function (FVC, FEV1, FEF25, FEF50, FEF75) were negatively associated with salivary cotinine; all coefficients were highly significant statistically. Only the ratio FEV1/FVC was not correlated with salivary cotinine."

Pages 6-35 and 6-36; Figures 6-1 and 6-2.
Remove Duff et al. study from Figure 6.1 and add it to Figure 6.2

Page 6-38: Insert before last sentence on the page

Bråbäck et al. (1995) undertook a cross-sectional study of 2,594 children, aged 10-12, in cities in Sweden, Poland, and Estonia, examining a variety of risk factors for respiratory symptoms and for atopic sensitization. The relevant odds ratios, derived from multiple logistic regression analysis, for "coughing attacks" (defined as either nocturnal cough lasting at least 4 weeks or exercise-induced cough) are presented in the following table:

	All	Sweden	Poland	Estonia
Maternal smoking				
1-9 cigarettes/day	1.55 (1.07-2.24)*	0.67 (0.25-1.78)	1.38 (0.52-3.70)	1.80 (1.15-2.80)**
>9 cigarettes/day	2.60 (1.69-4.01)***	1.40 (0.70-2.80)	2.88 (1.23-6.74)**	4.27 (2.04-8.91)***

*p<0.05, **p<0.01, ***p<0.001

There were findings of other significant associations between maternal smoking and respiratory symptom indices in Poland and Estonia, but not Sweden. The difference in results between Sweden and the other two countries may be related to the intensity of smoke exposure related to dwelling size and crowding, since most families in Poland and Estonia lived in apartments, while only about 1/3 of Swedish families did, and the average number of persons per room was 0.9 in Sweden, 1.7 in Poland, and 1.5 in Estonia. In addition, the authors noted that in Sweden there is widespread public awareness of health hazards associated with ETS exposure, leading many parents to smoke outdoors.

Cuijpers *et al.* (1995) undertook a cross-sectional examination of a variety of potential indoor environmental influences on respiratory symptoms and lung function in 535 Dutch children, aged 6 - 12. This study reported significant associations between ETS exposure and cough at 11-20 smokes per day in boys, but not at less than 11 or greater than 20 smokes per day, and no significant associations for girls. However, the numbers of symptomatic boys and girls were small (e.g., 33 and 26, respectively). The "significant" result for 11-20 smokes/day was based on a significance level of 0.10 rather than the more conventional level of 0.05. Examining the symptom of shortness of breath, Cuijpers *et al.* reported an exposure-response relationship for boys: the odds ratios for

<11, 11-20, and >20 smokes/day for maternal smoking were 1.61 (0.58-4.50), 2.80 (1.13-6.95), and 4.58 (1.19-17.65) (again with the significance level set at 0.10, so these represent 90% confidence intervals, which would be even wider had the investigators set $\alpha = 0.05$). While there was no relationship between paternal smoking and boys' symptoms, the odds ratio for <11 smokes/day for girls was elevated (2.85) and significant at $\alpha = 0.10$. In this study, it appears that boys might be more susceptible to ETS-related effects; however, because the numbers of children affected were so small, the confidence intervals are quite wide.

Moyes *et al.* (1995) was a cross-sectional investigation of asthma and allergy in 2,614 primary school and 2,752 secondary school children in six districts bordering the Bay of Plenty in New Zealand. They reported that parental ETS exposure was related to nocturnal cough, nasal symptoms, and wheeze in the older (ages 13-14) but not the younger (ages 6-7) children. The odds ratios for nocturnal cough and wheeze were highly significant ($p<0.01$). While this study does not have the same statistical power issues as that reported by Cuijpers *et al*. (1995), the analysis of passive smoking was crude (i.e., "Parental smoking" - yes/no, without stratification by maternal vs. paternal smoking or quantification of numbers of cigarettes smoked/day) and the only other variable adjusted for was ethnicity (European vs. Maori).

Forastiere *et al*. (1992) examined the relationships between a variety of predictors and respiratory illness in 2,929 Italian children, aged 7 - 11 years old, in a cross-sectional study in 1987, and found significantly elevated odds ratios in relation to the children's exposure to passive smoking. For example, the odds ratios (and 95% confidence intervals) for any smoker in the house were 1.3 (95% C.I. = 1.03-1.6) for early respiratory infection and 1.8 (95% C.I. = 1.2-2.7) for night cough. Though the odds ratios were elevated for either maternal or paternal smoking alone, they were not statistically significant.

Wolf-Ostermann *et al.* (1995) undertook a prospective cohort investigation of respiratory illness in 8,514 German children, with data collection in 1977, 1979 and 1985. They also found a variety of significantly increased odds ratios for several adverse respiratory outcomes; e.g., 1.26 (1.07-1.49) for bronchitis, and 1.55 (1.30-1.85) for fall and winter cough.

Mannino *et al*. (1996) analyzed data from the 1991 National Health Interview survey to estimate the relationships between parental smoking and the occurrence of respiratory illness in children aged 1-10 in the two weeks preceding the interview. They found that ETS-exposed children had 21% more restricted activity days, 31% more days of bed confinement, and 39% more days of school absence than those not exposed (all relationships were highly significant $p<0.01$). Adjusting for age, sex, family size, socio-economic status, season, and region, Mannino et al. found a higher incidence of acute respiratory illness (RR=1.10, 95%C.I. = 0.95-1.26) and a higher prevalence of chronic respiratory illness (OR=1.28, 95% C.I. = 0.99-1.67). Though these latter estimates were not statistically significant, Mannino *et al*. indicated that, because of the nature of the

survey, the study had a power of 0.30 to detect a 10% increase in the two-week incidence of acute illness and 0.60 to detect a 25% increase in the prevalence of chronic disease. The investigators also pointed out a variety of other considerations that would bias their results towards the null hypothesis, such as the dichotomous exposure classification (exposed vs. not exposed).

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Add to Section 6.2.3 after the paragraph describing the study by Cunningham *et al* (1995):

Casale *et al*. (1991), in a study of 143 Italian children aged 6-11, found dose-dependent relationships between several measures of lung function, particularly those related to airflow at low lung volumes, and ETS exposure. In this study ETS exposure was measured by both urinary cotinine and parental questionnaire. Goren and Hellman (1995), in a cross-sectional study of 8,259 Israeli second- and fifth-graders, found no relationship of parental smoking with measures of lung volume and of central or large airway caliber (FVC, FEV_1, PEF, and FEV_1/FVC). Guneser *et al*. (1994), in a study of 617 Turkish school children (287 boys and 330 girls), aged 9 - 12, found that all measures of lung function were lower in boys exposed to ETS compared with those who were not (with the exception of FEV_1 in 12-year olds), but that these differences were significant only for FVC in 9-year-olds, FEV_1 in 9- and 10-year-olds, peak flow in 10-year-olds, $FEF_{25\%}$ in 10-year-olds, $FEF_{25-75\%}$ in 9-year-olds. No data were presented for girls. Soyseth *et al*. (1995), in a study of parental smoking and asthma, bronchial hyperresponsiveness, and atopy in 620 Norwegian children aged 7 - 13, reported that, of the 573 children performing spirometry, there was a slight, but not statistically significant decrease in the FEV_1/FVC ratio (one measure of airway obstruction) in relation to maternal smoking (-0.7%), that was even less for paternal smoking (-0.2%). This was the only spirometry result reported in this paper. Cuijpers *et al*. (1995), in a study of 535 Dutch children aged 6-12, found significant decreases in several indices of lung function (FVC, FEV_1, PEF and $FEF_{25-75\%}$) in boys related to cumulative lifetime exposure to ETS, with larger decrements related to exposure during their entire lives versus part of their lives. As with respiratory symptoms, a lesser effect was seen in girls, with only one index ($FEF_{25-75\%}$) showing a similar trend that was significant. Finally, Richards *et al*. (1996), in a cross-sectional study of 395 South African adolescents aged 14-18, found no significant differences in FEV_1 and $FEF_{25-75\%}$ between exposed and non-exposed children.

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Insert before the second to last sentence in the top paragraph on the page

In this regard, the study by Cook *et al*. (1993) is instructive. In this investigation of 2,500 English and Welsh school children, aged 5-7, there were significant, consistent relationships between ETS exposure as measured by salivary cotinine and several indices of lung function. These associations were weaker and insignificant when based on questionnaire score, suggesting that this more commonly used method of exposure assessment may well result in a bias towards the null hypothesis.

Revisions to Chapter 7

Page 7-1

Add to the 7.0 Introduction:

The 1986 National Research Council report and a subsequent paper, Wald et al. (1986) pointed out that because smokers tend to marry smokers, if a study contains smokers who are misclassified as nonsmokers, they are more likely to be classified as exposed to ETS. Therefore, the estimate of relative risk to ETS exposure will be exaggerated due to the association of lung cancer with active smoking for this group of misclassified subjects. Wald et al. (1986) estimated the proportion of ever-smokers who are misclassified as lifelong nonsmokers to be about 7%. This estimate was based on the percent of self-reported nonsmokers (2.1%) who have levels of nicotine and continine in the range of those of smokers and the percent of smokers who on subsequent re-interview claimed to have never smoked (4.9%). Lee (1986, 1989, 1991) has argued that the extent of this misclassification bias is higher, about 12%. Two recent studies (Riboli et al., 1995; Nyberg et al., 1997), using different methodologies, conclude that, while there is some misclassification of smokers as nonsmokers, the misclassification rate is low and is unlikely to explain the lung cancer risk from ETS exposure. The study methods and findings from these studies are summarized below.

Riboli et al. (1995) reported the results of a multicenter (13 centers) international (10 countries) study organized by the IARC to validate self-reported exposure to ETS from different sources by analysis of urinary cotinine levels. Questionnaire data and urine samples were collected from 1,369 nonsmoking women who had not used any tobacco products for at least 2 years. Forty-seven women had urine cotinine levels above 50 ng/mg creatinine, a level used to discriminate smokers from nonsmokers in some previous studies. Further investigation of these 47 women showed that 27 had levels between 50-150 ng/mg while 20 had levels exceeding 150 ng/mg. In fact, the majority of women (16 of 27) with levels between 50-150 ng/mg had reported long daily exposure to ETS (i.e., > 5 hours per day) 4 to 8 days prior to sample collection and were exposed to at least 8 cigarettes per day. On the other hand, a significantly lower percent of women with cotinine levels exceeding 150 ng/mg had long daily exposure to ETS or were

exposed to at least 8 cigarettes per day. These investigators concluded that most of the women with levels between 50 to 150 ng/mg were truly heavily exposed to ETS while those with levels above 150 ng/mg were more likely to be deceivers and may have smoked. Thus the percent of deceivers (1.5%, 20 of 1,369) in this cross-sectional study is quite comparable to that reported by Fontham et al. (1994) in which 0.6% of lung cancer cases (2 of 356) (prescreened for smoking status on the basis of medical history and other factors) and 2.3% of population controls (25 of 1064) showed cotinine/creatinine concentrations of 100 ng/mg or higher. Results from this study also illustrate that cotinine levels between 50-150 ng/mg are quite plausible when nonsmokers are very heavily exposed to ETS.

Nyberg et al. (1997) investigated misclassification rates in two large Swedish cohorts in which smoking habits were assessed on two separate occasions some 6 to 10 years apart. Two types of misclassification rates were presented. The first misclassification rate was calculated based on the number of ever smokers misclassified as never smokers divided by the total population of ever-smokers. The second misclassification rate was calculated based on the number of reported never smokers who really were smokers divided by the total population of never smokers. In this study, the proportion of ever smokers misclassified as never smokers was 4.9% among men and 4.5% among women in the first cohort studies; the corresponding figures in the second cohort was 5.0% and 7.3%. The misclassification rate expressed as the proportion of never smokers who really were smokers was 11.1% in men and 1.3% in women in the first cohort study and 11.5% and 2.2%, respectively, in the second cohort study. Nyberg et al. (1997) noted that there is good agreement in most studies in terms of the first misclassification rate irrespective of geographic area or gender of subjects. On the other hand, the second misclassification rate is much more variable from study to study and that this rate can be misleading because it is dependent on the number of nonsmokers in a particular study. Aside from the rate of misclassification, these investigators also showed that in this, as in other study populations, most of the ever-smokers who were misclassified as nonsmokers had quit smoking some time earlier and smoked less than the average smokers. Thus, this study also suggested that there is limited smoker misclassification and that misclassification bias does not explain the lung cancer risk associated with ETS exposure.

Both of these studies suggest that to a large extent, misclassification of smokers as nonsmokers can be minimized if adequate screening questions are used to ensure that former smokers are identified and are excluded from studies of lifetime nonsmokers. Although cotinine is only a marker of recent tobacco exposure, it is still useful be able to exclude out current smokers from a study. In fact, multiple sources of information and carefully screening questions were used in many of the newer studies of ETS and lung cancer (such as Fontham et al. [1994]) so that this source of misclassification bias has been minimized. The varying degrees of misclassification bias among the studies in the US EPA meta-analysis of ETS exposure and lung cancer were recognized by the agency, and adjustments applied were consequently specific to the individual studies (US EPA, 1992, Appendix B).

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(7.2.3 ETS Exposure from Spouses)

The results from these four recent U.S. studies are compatible with the pooled estimate of the U.S. EPA (1992) report, which found a summary OR of 1.19 (90% CI=1.04, 1.35) for ever exposed to ETS from spouses (for U.S. studies). Results from the largest population-based study, the U.S. multicenter study (OR=1.29, 95% CI=1.04, 1.60, for ever exposed) (Fontham *et al*., 1994) were closest to the pooled estimate from the U.S. EPA report. Of the two other population-based studies, the association found in the Florida study (Stockwell *et al*., 1992) was stronger (OR=1.6, 95% CI=0.8, 3.0; although it did not achieve statistical significance except for the highest exposure category: OR=2.4, 95% CI=1.1, 5.3), and that from the Missouri study (Brownson *et al*., 1992) was weaker (overall OR=1.0, 95% CI=0.8, 1.2; for highest exposure category of spousal smoking, OR=1.3, 95% CI=1.0, 1.7) than the pooled estimate result. Although the authors of the fourth study, the hospital-based case-control study (Kabat *et al*., 1995), ~~-~~reported ~~interpreted~~ their findings ~~(analyzing men and women separately)~~ to be unsupportive of an association between ETS exposure and risk of lung cancer, the odds ratios were elevated for males (OR=1.60 95%CI 0.60, 1.94) and females (1.08, 95%CI 1.08, 95%CI 0.60, 1.94), ~~we calculated from their results (OR [for males and females combined] = 1.19, 95% CI=0.76, 1.87),~~ though not statistically significant, and the results of this small study do no contradict an increased risk of order 20%.~~, was in fact very similar to the pooled estimate from the U.S. EPA report~~. In addition, positive increasing trends in risk of lung cancer in nonsmokers were observed for increasing ETS exposure indices in all three of the population-based studies (Table 7.5). The concordance in these study results gives further credibility to the finding of a causal association between spousal ETS exposure and risk of lung cancer described in the U.S. EPA (1992) report.

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will add sentence on confounding from Fontham et al.

Page 7-25

(7.2.5 Summary)

Despite the compelling biologic plausibility of an effect of ETS exposure on risk of lung cancer, detection of an effect has been problematic because a small excess in risk is difficult to establish in a single epidemiologic study. The U.S. EPA (1992), NRC (1986) and Surgeon General (U.S. DHHS, 1986) all undertook comprehensive reviews of the literature and determined on the basis of the overall evidence that ETS exposure causes lung cancer. Since the publication of the most recent authoritative review of lung cancer and ETS exposure (U.S. EPA,1992), three large U.S. population-based studies (Stockwell *et al*., 1992; Brownson *et al*., 1992; Fontham *et al*., 1991 and 1994) and a smaller hospital-based case-control study (Kabat *et al*., 1995) have been published. The three population-based studies were designed to and have successfully addressed many of the weaknesses (*i.e.*, small sample size, possible selection bias, possible misclassification

biases, inadequate adjustment for potential confounders) for which the previous studies on ETS and lung cancer have been criticized. Results from these studies are consistent with the conclusions of the U.S. EPA (1992), NRC (1986) and Surgeon General (U.S. DHHS, 1986) reports. Each of the three population-based studies show a statistically significant increased risk of lung cancer in nonsmokers associated with long term exposure to ETS as well as increasing risk with increasing ETS exposure. The smaller hospital-based study lacked the statistical power to find the effect observed in the other studies. ~~However, though not statistically significant, the OR we calculated for male and female combined in this study was similar to that reported by the U.S. EPA.~~ Taken together, the recent studies provide additional evidence that ETS exposure is causally associated with lung cancer. The consistency of the findings in the four recent studies and the meta-analysis result of the U.S. EPA indicates about a 20% increased risk of lung cancer in nonsmokers.

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(7.3.1.2 ETS and nasal sinus cancer)

The role of ETS exposure in the etiology of nasal sinus cancer in nonsmokers has been investigated in one cohort and two case-control studies (Table 7.8).

Hirayama (1983, 1984)

Using data from a Japanese prospective study (see Section 7.1 for detailed description), Hirayama (1983, 1984) reported an increased risk of para-nasal sinus cancer (based on 28 nasal sinus cancer deaths) among nonsmoking women exposed to husbands' smoking. Relative risks increased with amount husbands smoked: compared to women married to nonsmokers, the RR was 1.7 (95% CI=0.7,4.2), 2.0 (95% CI=0.6,6.3), and 2.6 (95% CI=1.0, 6.3; $p < 0.05$), for women whose husbands smoked 1-14, 15-19, and 20+ cigarettes per day respectively, ~~when~~ husbands' age and occupation ~~were adjusted for~~. The dose-dependent increase in risk was significant ($p < 0.03$). Active ~~However,~~ smoking was not associated with nasal sinus cancer in this study; the OR ~~associated with active smoking~~ was 0.9 (90% CI=0.5-1.4) for males and females combined (Hirayama, 1990). Cell type distribution of nasal sinus cancer in nonsmokers and smokers was not available in this Japanese cohort study.

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(7.3.1.3 Summary)

Existing studies consistently show a significant positive association between exposure to ETS and nasal sinus cancer in nonsmokers. The results have been observed in studies ~~conducted in eastern and western countries,~~ in white American males and Japanese females, in cohort and case-control study designs, and with some adjustment for possible confounders. The significant risks associated with ETS exposure ranged from 1.7 to 3.0.

Page 7-35 (added 3rd paragraph)

The above epidemiologic studies investigated the risk of breast cancer in active smokers compared to all nonsmokers in the baseline group. A recent study (Morabia et al., 1996) investigated the effect of active smoking compared to nonsmokers not exposed to ETS. Data were also presented which allowed comparison of the effect of active smoking compared to all nonsmokers and to nonsmokers not exposed to ETS. We calculate that compared to all nonsmokers (126 cases and 621 controls), the crude ORs associated with ever smoking 1-9, 10-19, and 20+ cigarettes per day were 1.1, 1.5, and 1.6, respectively (p trend = 0.007). The corresponding adjusted ORs when compared to nonsmokers not exposed to ETS (28 cases and 241 controls) were 2.4, 3.6, and 3.7 (p trend = 0.09) (from Table 2 of Morabia et al., 1996). Similar results were obtained when current active smokers were compared to all nonsmokers and to nonsmokers not exposed to ETS.

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Hirayama (1984)

The first study was a Japanese cohort study (Hirayama, 1984) which included 115 breast cancer deaths in never smoking women. Nonsmoking women whose husbands smoked showed a small, nonsignificant increased risk of breast cancer (RR = 1.3, 95% CI = 0.8 - 2.0). ~~The increased risk associated with ETS exposure was observed only in Japanese women less than 59 years old but not in older women (Wells, 1991).~~

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Results on the association between passive smoking and risk of breast cancer were presented for smokers and nonsmokers combined. There was some suggestion that risk was highest among individuals who were exposed to ETS during both childhood and adult life. Compared to women who were not exposed to ETS, exposure during childhood only, adult life only, and during both childhood and adult life were associated with ORs of 1.98 (95% CI=0.35-11.36), 2.65 (95% CI=0.80-8.83), and 3.13 (95%

CI=1.05-9.38), respectively. Although there was an increased risk of breast cancer associated with childhood ETS exposure, adult exposure to ETS from partners, from other smokers at home and at work, and total lifetime exposure, there was no consistent dose trend of increasing risks with increasing levels of any of these sources of ETS exposure. ~~The findings on ETS exposure and risk of breast cancer in nonsmokers were not presented separately.~~ However, the investigators noted that the passive smoking findings among nonsmokers were similar to those for smokers and nonsmokers combined. The relative risks were consistently elevated but again there was no evidence of a significant dose response for any exposure variable.

Changes to Table 7.4 (in underline and strikeout)

	Stockwell et al. (1992)	**Brownson et al. (1992)**	**Fontham et al. (1994)**	**Kabat et al. (1995)**
Matching variables of lifetime nonsmoking controls	NA	age	age, area, & race ~~ethnicity~~	age, race, hospital, date of interview
Biological markers	none	none	urinary cotinine***	none

*** on 81% of self-respondent cases and 85% of controls

Changes to TABLE 7.6 (in underline and strikeout)

Janerich et al. (1990) /New York	M, F	Smoker-years in childhood/adolescence 0 1-24 25+	 ~~3~~57 68 82 94 52 29	 1.0 1.09 (0.68-1.73) 2.07 (1.16-3.68)
Fontham et al. (1994) /Five U.S. areas	F	During childhood father no yes mother no yes Childhood household exposure (in yrs.) 0 1-17 18+	 304 ~~699~~ 669 299 556 76 161 548 1079 148 444 95 291 146 485	 1.00 0.83 (0.67-1.02) 1.00 0.86 (0.62-1.18) 1.00 0.99 (0.73-1.35) 0.88~~9~~ (0.67-1.16)
~~Kabat et al. (1990)~~	~~M~~ ~~F~~	~~Family member smoked~~ ~~no~~ ~~yes~~ ~~no~~ ~~yes~~	 ~~15 36~~ ~~21 69~~ ~~17 61~~ ~~36 77~~	 ~~1.00~~ ~~0.73 (0.34-1.59)~~ ~~1.00~~ ~~1.68 (0.86-3.27)~~
Wu-Williams et al. (1990) /North China	F	father smoked no yes mother smoked no yes	 235~~335~~352 182 250 298 410 119 192	 1.0 1.1 (0.8-1.4)* 1.0 0.9 (0.6-1.1)*
Pershagen et al. (198~~6~~7) /Sweden	F	parents smoked neither parent smoked one or both parents smoked	 ~~9~~ 38 ~~18~~NA** ~~38~~ 9 ~~76~~NA	 1.0 1.0 (0.4-2.3)**

*Calculated from data provided in the study publication

**The numbers presented are shown in table 5 of Pershagen et al. (1987). Although the numbers (and %) of cases and controls with at least one parent smoker are shown in Table 2 of Pershagen et al. (1987), we cannot reproduce the OR of 1.0 shown in their Table 5 if we impute the number of controls by parents smoking habits.

Changes to Table 7.7 (in underline and strikeout)

Study/ Year of study	Questions on ETS exposure	#unexposed/ #exposed cases	#unexposed/ #exposed controls	OR (95% CI) for exposed
Janerich et al. (1990) 1982-84	# smokers at work (lifetime), amount of time working with smokers	NA	NA	no association 0.91(0.8-1.04)
Kalandidi et al. (1990) 1987-89	current/last job #smokers at work	24/65	40/78	1.39 (0.8-2.5)d
Koo et al. (1987~~7~~4) 1981-83	any ETS exposure at work (all jobs)	NA	NA	0.91(0.15-5.37)
Wu-Williams et al. (1990) 1985-87	exposure at each job	187/23~~0~~28	301/301	1.2 (0.9-1.6)[e] 1.06 (0.8-1.4)[f]

[d]Calculated from entries on exposure at work in Table 2 of publication
[e]Adjusted for center, age and education,
[f]Adjusted for center, age, education, previous lung disease, and heating practices

TABLE 7.9
RELATIONSHIP BETWEEN ACTIVE AND PASSIVE SMOKE EXPOSURE AND RISK OF CERVICAL CANCER

Study	# Cases/# Controls Cervical Cytology (among cases)	Active Smoking (Among Never Smokers)			Passive Smoking		
				Adj. OR[a]			
Hirayama (1981, 1990)	Total number of cervical cancer deaths was 589; number of cervical cancers in never smokers was 250	Ever smoked		1.6 (1.3 - 1.9)	NS		1.0
		1 - 9 cigarettes/day		1.7 (1.3 - 2.3)	Ex/1-19/day		1.15
		10 - 19		1.3 (1.0 - 1. 8)	≥20/day		1.14[b]
		20+		2.4 (1.4 - 3.9)			
Sandler et al., 1985a, 1985e	56 cervical cases among nonsmokers -data on nonsmoking controls not presented (there were a total of 330 female controls)				Exposed to Spouse's smoking	CA/CO NA	2.1 (p<0.05)
					Mother smoking	no 37/196[c]	1.0
						yes 3/24	0.7 (0.2 - 2.3)
					Father smoking	no 15/120	1.0
						yes 19/91	1.7 (0.8 - 3.4)
			CA/CO	Adj. OR[d]	Hrs/day[e]	CA/CO	Adj. OR[d]
Slattery *et al.*, 1989	266 cases/408 controls (cases: 78% carcinoma in-situ, 22% invasive cancer)	Never	81/305	1.0	None	NA	1.0
		Ex-smoker	37/48	1.4 (0.8 - 2.5)	0.1 - 0.9	NA	1.1 (0.5 - 2.9)
		Current smoker	148/55	3.4 (2.1 - 5.6)	1.0 - 2.9	NA	1.6 (0.5 - 4.7)
					≥3.0	NA	3.4 (1.2 - 9.5)

TABLE 7.9 (CONTINUED)
RELATIONSHIP BETWEEN ACTIVE AND PASSIVE SMOKE EXPOSURE AND RISK OF CERVICAL CANCER

Study	# Cases/# Controls Cervical Cytology (among cases)	Active Smoking (Among Never Smokers)	CA/CO	Adj. OR[f]	Passive Smoking	CA/CO	Adj. OR[f]
					At Home		
					Yrs Exposure		
Coker *et al.*, 1992	103 cases/268 controls (All biopsy-confirmed cervical intraepithelial neoplasia, class II or III)	Never	37/170	1.0	Not exposed	9/49	1.0
		Ever smoked	66/96	1.7 (0.9 - 3.3)	<17 yrs	18/52	1.5 (0.5 - 4.0)
		Current smoker	66/49	3.4 (1.7 - 7.0)	≥18 yrs	9/69	0.4 (0.1 - 1.3)
					At work		
					Yrs Exposure		
					Not exposed	28/132	1.0
					1 - 4 yrs	6/21	1.7 (0.5 - 5.1)
					≥5 yrs	2/16	0.4 (0.1 - 2.5)

a 90% CI.
b p value was 0.25.
c Number of cases and controls was calculated from Table 4 of Sandler et al., 1985e.
d Adjusted for age, church attendance, education, and number of sexual partners of the women.
e Number of hours of exposure per day inside and outside of the home.
f Adjusted for age, years of education, race, number of pap smears, number of partners, and genital warts.

Abbreviations: NA = not available, CA/CO = cases/controls, OR = odds ratio.

Revisions to Chapter 8

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Wells' 1994 review included results from 13 studies; eight of these studies were not included in his 1988 review (Hole *et al.*, 1989; Humble *et al.*, 1990; Butler, 1988; Dobson *et al.*, 1991a; He *et al.*, 1994; La Vecchia *et al.*, 1993; Jackson, 1989; Sandler *et al.*, 1989 (this covered the same study as Helsing *et al.*, 1988~~Svendson *et al.*, 1987~~). Pooled risk estimates for CHD morbidity and mortality in relation to ETS exposure for males and females separately and combined were presented. Risk estimates were presented with and without correction for misclassification bias of smokers as nonsmokers. In women the OR was 1.51 (95% CI=1.2-2.0) for CHD morbidity and 1.23 (95% CI=1.11-1.36) for CHD mortality in association with ETS exposure. The corresponding ORs in men were 1.28 (95% CI=0.91-1.81) and 1.25 (95% CI=1.03-1.51). The ORs for CHD morbidity and mortality in women and men were almost unchanged after correction for misclassification bias.

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As pointed out by Steenland *et al*. (1996) and Glantz and Parmley (1996), ETS exposure may have both acute and chronic effects on the heart. The emphasis of LeVois and Layard on 'any' (*i.e*., current and former) ETS exposure from spouses and exposure from spouses who were former smokers strongly biased the results toward the null. First, results for 'any' ~~spousal~~ exposure to spousal ETS diluted the effects associated with exposure to current smokers by in~~ex~~cluding exsmokers. This is evident when one compares the RRs associated with any ETS exposure versus the RRs associated with amounts currently smoked by spouses (Table 4 of LeVois and Layard, 1995) (RRs associated with any current smoke exposure were not presented and could not be computed on the basis of the data presented). The RRs associated with any ETS exposure was less than 1.0 for men (RR=0.97) and close to 1.0 for women (RR=1.0 and 1.03) in the CPS I and CPS II analyses. However, almost all the RRs associated with each exposure category (based on amount currently smoked by spouses: 1-19, 20-39, 40+ cigarettes per day) were above 1.0 for women in both CPS I and CPS II and for men in CPS II. In fact, in the CPS II analysis, five of the six RRs associated with varying amounts smoked by spouses were above 1.13. These RRs by amounts currently smoked by spouses suggest that the RR for any exposure to current smokers is above 1.0. Second, the effect of exposure from former smokers may be negligible, similar to the rapid reduction in heart disease risk seen among active smokers upon cessation of smoking.

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(8.3.2 Endothelium Function)

Endothelial dysfunction is considered an important marker of early vascular damage. Celermajer *et al.* (1996) conducted a study which compared the endothelial function in the arteries of three groups of healthy teenagers and young adults: active smokers (n=26), lifelong nonsmokers who were exposed to ETS (passive smokers) (n=26), and lifelong nonsmokers who reported to have never been regularly exposed to ETS at home or at the workplace (n=25). Regular exposure to ETS was defined as self-reported exposure at home or at work or both for at least one hour per day for at least three years.

Vascular reactivity of the brachial artery was analyzed. The ultrasound method was used to measure brachial artery vascular responses to increased flow (an endothelium-dependent dilator stimulator) and to nitroglycerin (an endothelium-independent dilator). The diameter of the vessel was measured in every case by two independent observers who were blinded to the active and passive smoking status of the study subjects. Flow-mediated dilatation and nitroglycerin-induced dilatation were calculated by each observer, and the average results of the two observations were recorded.

Subjects in the three groups were similar in baseline characteristics including their age, systolic and diastolic blood pressure, total cholesterol, low-density and high-density lipoprotein cholesterol, vessel size at rest, and flow at rest. Not unexpectedly, the salivary cotinine levels (ng/ml) were significantly higher in the active smokers (170 ng/ml) compared to the passive smokers (3.7 ng/ml) and the nonsmokers (1.2 ng/ml).

The degree of reactive hyperemia produced by cuff inflation and release was similar in the three groups studied. In response to this increase in flow, arterial dilatation was 8.2 percent in the nonsmokers, 3.1 percent in the passive smokers, and 4.4 percent in the active smokers. Among the passive smokers, the percent flow-mediated dilatation was 4.1 in the subjects with light exposure to ETS, 3.1 in those with moderate exposure to ETS and 1.8 in those with heavy ETS exposure. There was no difference in the nitroglycerin-induced dilation in the three groups.

In this study passive smokers have significantly impaired arterial endothelial function. Impaired bioavailability of nitric oxide, the endothelium-derived relaxing factor, may be particularly important, since nitric oxide acts to inhibit platelet aggregation (Cooke and Tsao, 1994; Deanfield, 1996). Dilatation mediated by brachial-artery flow is endothelium-dependent and is mediated in part by the release of nitric oxide. The activity of endothelial nitric oxide may be impaired in young passive smokers as well as in active smokers. However, a mechanism based on the destruction of nitric oxide by oxidant gases in ETS is questionable given the limited potential for exposure because of the highly reactive nature of oxidant gases which would lead to their dissipation in the environment. Although only superficial systemic arteries can be studied with this ultrasound-based method, endothelial dysfunction in the brachial artery appears to be well correlated with both coronary endothelial physiology and coronary atherosclerosis.

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Nicotine is a potential cause of the observed changes in endothelial cells and platelet aggregate ratios after smoking tobacco cigarettes, although other components of cigarette smoke may ~~also~~ be important. The modest changes in endothelial cells and platelet aggregate ratios after exposure to ETS may~~are likely to~~ be related to the increase in nicotine and carboxyhemoglobin levels in the blood after exposure to ETS. The changes observed in relation to smoking non-tobacco cigarettes may be explained by the release of small amounts of catecholamines and modest elevation in nicotine levels even when non-tobacco cigarettes are smoked (Davis *et al.*, 1990). These studies demonstrate that brief exposure to ETS under naturally occurring environmental conditions has consistent acute effects on the endothelium and platelets similar to those of active smoking. The exact roles of carbon monoxide, nicotine, and other components of tobacco smoke as causes of observed effects on platelets and the endothelium remain unclear; however, both of the effects seen following exposure of nonsmokers to ETS, platelet activation and endothelial damage, are prominent among the mechanisms thought to be involved in atherosclerosis and arterial thrombosis. These observations suggest another mechanism whereby exposure to ETS may increase the risk of heart disease in nonsmokers.

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